

ANIMAL MODEL  
FOR  
HUMAN DISEASE

Adenocarcinoma

**Animal Model:** Spontaneous  
Adenocarcinoma in Aged Rabbits

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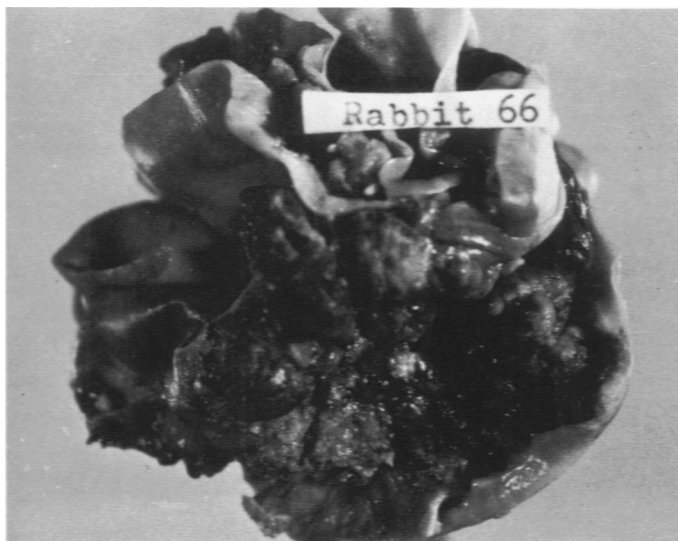
**Biologic Features**

Among various mammalian species investigated,<sup>1,2</sup> the incidence of spontaneous endometrial carcinoma was especially high in rabbits.<sup>3</sup> The most extensive study of these tumors was made by Greene *et al*,<sup>4,5</sup> who found 142 adenomas and adenocarcinomas in a colony of 849 rabbits observed for 9 years. Of the 14 breeds in this colony, the following showed appreciably higher incidences: Tan, 50%; French Silver (Champagne), 25%; Havana, 22%; and Dutch, 20%. Incidences in other breeds varied from 8 to 17%. Certain constitutional abnormalities and toxemia of pregnancy were associated with higher incidences of neoplasms.<sup>6</sup> Thirty-seven percent of tumor-bearing animals had second primary tumors elsewhere.<sup>7</sup> Ingalls *et al*<sup>8</sup> discovered 353 uterine tumors among 1735 rabbits of the Phipps colony, which was observed for 30 years. The incidence of tumors increased with age, reaching approximately 60% in animals over 4 years of age, in both colonies cited, and 79% in Greene's colony of 5-year-old animals.

We studied 117 Dutch rabbits for 30 months. This breed was chosen because it is available commercially in larger numbers than other breeds. The uteri of 83 rabbits were examined microscopically and 3 atypias (4%), 2 adenocarcinomas *in situ* (3%), 14 invasive adenocarcinomas (17%) and 1 leiomyosarcoma (1%) were found. Most of the tumor-bearing animals were 4 to 7 years old. The adenocarcinomas were often multicentric, involving both uterine horns. The tumors were polypous, with frequent central ulcerations (Figure 1). The uterine horns were distended with the tumor and hydro- and pyometra from neo-

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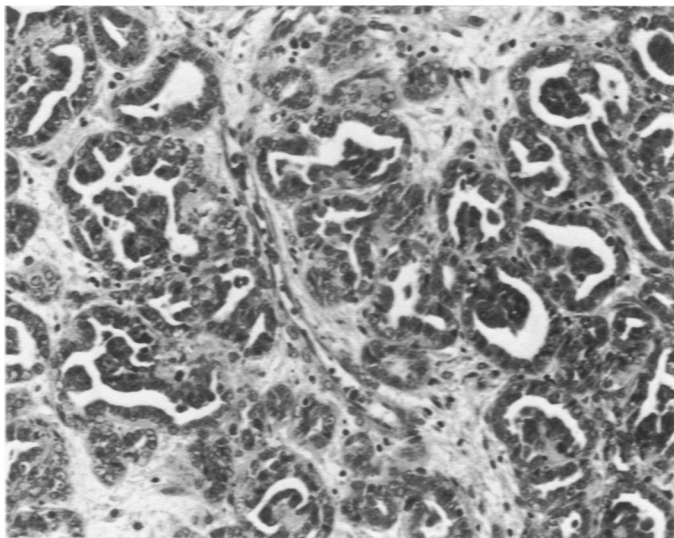
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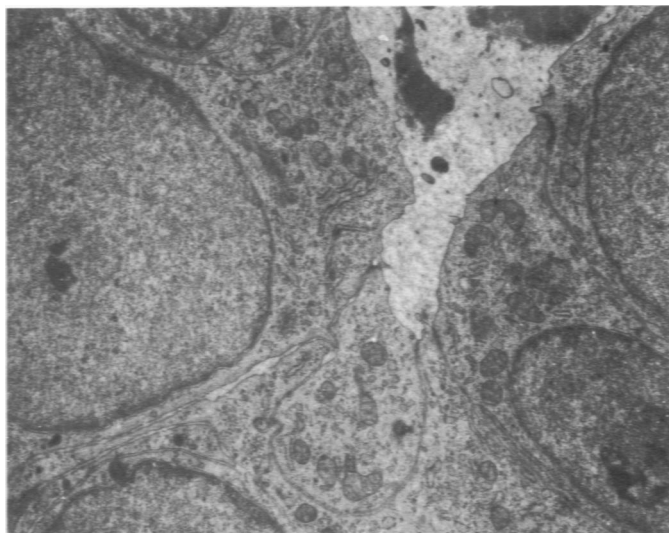
**Fig 1**—Gross appearance of an endometrial carcinoma. A markedly distended, thin-walled uterine horn contains a polypous tumor with central ulceration.

plastic obstruction of the lumen were observed. Carcinomatous dissemination on the peritoneal surface was observed in 3 animals. Pulmonary metastasis was noted from one carcinoma and one sarcoma. Histologically, the carcinoma was a well-differentiated adenocarcinoma (Figure 2) originating from the deeper glandular portion of the epithelium. Electron microscopically, the cells of the adenocarcinoma showed prominent nuclei and nucleoli, loss of secretory vesicles and cilia, and marked simplification of cytoplasmic organelles (Figure 3).<sup>9</sup> Histochemically, no alkaline or acid phosphatase activity could be demonstrated in either epithelial or stroma cells within adenocarcinomatous nodules.<sup>10</sup> Unlike normal endometrium, estrogens did not stimulate alkaline phosphatase actively in cancer cells but did elicit moderate acid phosphatase activity in malignant cells. Dysplasia and carcinomas *in situ* appeared in deeper portions of endometrial glands in association with severe senile atrophy of the endometrium. No association with glandular or cystic hyperplasia was recognized. Dysplasia and carcinoma *in situ* were not clearly differentiated, but many more atypical glands were present in the *in situ* stage. These lesions were characterized by irregularly distributed glands with advanced cellular atypia. Electron microscopic study of *in situ* carcinomas revealed lack of cilia and secretory vesicles, increased intercellular spaces and abundant lysosomes. Ultrastructurally, the cells of invasive and carcinomas *in situ* resembled those of severe senile atrophy of the endometrium in their loss of cilia and secretory vesicles and in the simplification of cytoplasmic structure. There was little ultrastructural resemblance between these lesions and glandular or cystic hyperplasia. Interestingly, estrogen, ad-

**Fig 2**—The carcinoma is a well-differentiated adenocarcinoma with infiltrating glands, often with papillary projections (X 170).



**Fig 3**—Electron micrograph of carcinoma cells which show large nuclei and a small amount of cytoplasm. The cilia and secretory vesicles seen in normal endometrial cells are absent. (X 10,000).



ministered to aged Dutch rabbits, reduced the incidence of endometrial carcinomas from 17 to 3%, Greene<sup>11</sup> transplanted the tumor into the anterior eye chamber of rabbits and commented that its neoplastic behavior was in no way related to the histologic appearance of the implants.

#### **Comparison with Human Disease**

Generally, human endometrial carcinoma is associated with glandular hyperplasia; rabbit carcinoma is associated with senile atrophy. Constitutional abnormalities, such as dwarfism and toxemia of pregnancy, were associated with endometrial carcinoma of the rabbit as often as

diabetes, obesity and hypertension are associated with endometrial carcinoma of humans. While the relationship between hyperestrinism and human endometrial carcinoma remains controversial, senescence of the endometrium seemed important in spontaneous adenocarcinoma of the endometrium of rabbits; the administration of estrogens appeared to reduce the number of tumors. In humans, cessation of menstruation is related to the incidence of endometrial carcinoma and hormonal dysfunctions, such as the Stein-Leventhal syndrome, have been associated with endometrial carcinoma in young patients.

#### Potential Use

Further metabolic and endocrinologic studies on the carcinogenesis of endometrial carcinoma of rabbits will contribute greatly to the elucidation of the human counterpart.

#### Availability

The major rabbit colonies cited in this report were kept in the Departments of Pathology of Yale University,<sup>4</sup> The Ohio State University<sup>3</sup> and Henry Phipps Institute of the University of Pennsylvania;<sup>8</sup> however, the colonies are no longer being maintained. In our experience, female Dutch rabbits 2 to 3 years of age can be collected from commercial sources, and within 1 to 2 years investigators should obtain a number of spontaneous endometrial adenocarcinomas.

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